experiments, the effect of vitamin A was observed only in healthy animals exposed to no stress other than that of the viral inoculation, anesthesia, and sham-burn injury. When burn disease was induced or when biochemical stress (Depo-Medrol®) was administered, a salutary effect of vitamin A was not observed.

[21] The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

[22] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care.", as promulgated by the Committee on the guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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Summary. High doses of vitamin A decreased the severity of tumor development in mice inoculated with a murine sarcoma virus; the same doses of vitamin A had no effect on the increased tumorigenesis seen in animals severely stressed with thermal injury or the increased tumorigenesis induced by exogenous glucocorticoid administration[21].

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Embryonic Death in Mouse due to Lead Exposure

Lead exposure represents a particular hazard to pregnancy. Sterility, abortions and high fetal and neonatal loss in female lead workers were observed more than 100 years ago[1], and for a time, lead enjoyed popularity as a mean to induce criminal abortions, a procedure which quite often gave raise to serious intoxication[2]. The data on experimental animals are contradictory in that some authors observed reduced fertility even after exposure to low doses, whereas others did not. Thus, SCHROEDER et al.[3,4] supplied lead at a level of 25 ppm to rats and mice over a period of 3 generations and reported fewer litters and early death at tissue levels which were only 2 to 3 times greater than those in controls. On the other hand, LÉONARD et al.[5] giving up to 1000 ppm of lead in the drinking water for 9 months, could not find a significant difference in fertility of mice, and this agrees with the results of AZAR et al.[6] and JESSUP[7] in dogs and rats.

Similar disagreements exist with respect to a possible teratogenic action of lead in experimental animals. Hamsters[8] display an increased rate of malformations, particularly in the tail region, when the mothers are injected with 50 mg/kg of lead on the 8th day of pregnancy. FOURNIER and ROSENBERG[9] could, however, not note any malformation in rabbits or rats after somewhat lower doses (a total of 16 mg/kg), and similar observations have been reported for the cow[10] and the sheep[11]. In view of these disagreements, we have investigated the effects on the pregnancy of different doses of lead acetate added to the diet.

Material and methods. Young adult mice of the C57Bl strain raised in our laboratory were utilized. 3 females were caged with 1 male from the beginning of the week and examined daily for the presence of vaginal plugs. Females with vaginal plug were removed and immediately

Table I. Results of the dissections (16–18 days after the vaginal plug)

Lead [% in diet]	Pregnant females[a]	Corpora lutea	Live embryos	Dead embryos	Loss before implantation
0	26	352	216 [8.31]	32 [1.23]	104 [4.00]
0.125	28	381	231 [8.25]	41 [1.46]	109 [3.89]
0.250	11[c]	138	91 [8.27]	21 [1.91]	26[b] [2.36]
0.500	8[c]	92	60 [7.50]	19[b] [2.38]	13[c] [1.63]

[a] 50 mice with vaginal plug were utilized in each group. Values in brackets are mean numbers per pregnant female. [b] Significant at $p \leqslant 0.05$ level. [c] Significant at $p \leqslant 0.01$ level compared to the controls in the χ^2 test.

Table II. Weight of the embryos (mean in mg $\pm$ SE)

Lead [% in diet]	Days of pregnancy 16	17	18
0	389 ± 11	617 ± 16	978 ± 21
0.125	375 ± 14	605 ± 15	922 ± 15[b]
0.250	406 ± 11	587 ± 23	850 ± 17[c]
0.500	312 ± 36[b]	331 ± 15[a, c]	793 ± 33[c]

[a] These embryos were obtained from only 1 mouse. [b] Significant at $p \leqslant 0.05$ level. [c] Significant at $p \leqslant 0.01$ level compared to controls in t-test.

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placed on a diet containing 0, 0.125, 0.25 or 0.50% of lead. Mating was discontinued during week-end. A total of 50 females were used in each group. The mice were dissected on day 16–18 following observation of the vaginal plug, and the number of corpora lutea and of dead and live embryos was recorded. The weight of the live embryos was also determined. Loss prior to implantation is represented by the difference between the number of corpora lutea and that of implanted (live + dead) embryos. The results of the experiments were evaluated by the χ^2 or the t-test.

Results and discussion. The data shown in Table I demonstrate that lead treatment reduces significantly the incidence of pregnancies (mother with at least 1 implant) among females exhibiting vaginal plug. This effect becomes noticeable from doses of 0.25% of lead upwards. Among such pregnant females, the following effects of lead can be noted (Tables I and II): 1. Lead treatment increases significantly the number of embryos dying after implantation, an effect being conspicuous only for 0.5% of lead. 2. The number of embryos dying before implantation decreases after lead treatment with doses of 0.25% or more, so that the total number of embryos implanted per pregnant female increases slightly when related to the number of corpora lutea found. 3. A difference in the weight of live embryos becomes apparent during the last days of pregnancy. This effect is stronger for doses of 0.5% of lead. 4. No gross abnormalities were seen in the lead-treated embryos. This however, does not exclude the possibility that more subtile malformations were present, a problem which will be the object of further study.

Our data confirm the observations of LÉONARD et al.[5] in the mouse, but are at variance with those of SCHROEDER and MITCHENER[3], in that an effect of lead on fertility is seen only after rather high doses. The data obtained suggest that two types of effects of lead on fertility should be distinguished, those on the embryo and those on the mother.

The action on the embryo involves retardation in growth and eventually death at an advanced stage of pregnancy, as shown by the decrease in weight of surviving embryos and the increase in number of embryos dying after implantation. The increase in the number of animals with vaginal plug but no implant could result from the action upon the mother, diminishing her ability to maintain pregnancy. This elimination of the most sensitive females could explain that in the other females (with at least one implant), the preimplantation loss diminishes when compared to that of the controls.

Further studies must show whether this failure is due to a hormonal deficiency, an abnormal placenta or other factors[12].

Summary. Female mice which displayed a vaginal plug after mating were given a diet containing 0, 0.125, 0.250, 0.500% of lead as lead acetate and were dissected 16 to 18 days later. Lead treatment was found to reduce significantly the incidence of pregnancies and to increase the postimplantation loss in the pregnant females.

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Effect of Ethanol Intake on Phenytoin Metabolism in Volunteers

Phenytoin is one of the major antiepileptic drugs. Knowledge about the influence of ethanol intake on its metabolism would be useful for clinical management of the patient with epilepsy. In chronic alcoholics, elimination of phenytoin from plasma after oral dosage is significantly faster as compared with controls. Reduced absorption and induction of enzymes hydroxylating phenytoin have been implicated[1].

It is not known whether acute ethanol ingestion influences phenytoin metabolism in man. It is the purpose of this study to obtain information in healthy volunteers about the effect of acute ethanol intake on the elimination of phenytoin from plasma after a single intravenous dose.

Methods. The 3 female and 2 male volunteers, aged 22 to 47 years, had taken no drugs or alcohol during the 2 preceding months, and were considered healthy according to clinical history and routine laboratory tests. A single i.v. dose of 3 mg/kg phenytoin was injected slowly over 10 min. This was repeated after 7 weeks. At this time, the subjects were administered 1 g/kg ethanol in 40% rum in a sweet drink within 2 h after i.v. injection of 3 mg/kg phenytoin. Plasma samples were taken before and 2, 4, 8, 12, 24 h after the injection of phenytoin. Phenytoin[2] and ethanol[3] plasma concentrations were determined by gas-liquid chromatography in double determinations. The decline of the log phenytoin concentration in plasma with respect to time appeared linear about 4 to 8 h after injection in all subjects. The half-life ($t_{1/2}$) was calculated from the linear part of the curve by the method of least squares. Statistical analysis compared the slope and the elevation of the regression lines in each subject with and without ethanol present in blood.

Results. The average half-life of phenytoin was 12.4 h (SD $\pm$ 4.4) in our volunteers with no ethanol in their blood. After ethanol ingestion, the average half-life of phenytoin was 12.3 h (SD $\pm$ 5.2). The half-life of phenytoin in each subject with and without ethanol in his system was not statistically different at the 5% level (Table). 10 min after the i.v. injection, the phenytoin concentrations ranged from 2.7 to 7.5 µg/ml in the 5 subjects. Blood alcohol levels reached peak values of 0.53–0.80‰ about 1 h after the last intake of alcohol and disappeared linearly with time.

Discussion. The elimination of phenytoin from plasma after a single i.v. dose was monoexponential from about 4 to 8 h after drug administration in all subjects, a finding consistent with apparent first-order elimination kinetics. Ethanol intake with blood levels in a range of 0.53 to 0.80‰ did not influence the half-life of phenytoin in our volunteers. The half-life in the same subject with no ethanol in his blood, determined several weeks before

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